Remarks

Reconsideration of this Application is respectfully requested. The foregoing amendments place the specification and claims in condition for allowance or remove issues for appeal. Entry is respectfully requested.

The amendment to the specification is based upon an example provided by the Examiner in related U.S. Appl. No. 09/245,025, filed February 5, 1999. The claim amendments correct obvious typographical errors. These amendments to the specification and claims introduce no new matter, and their entry is respectfully requested.

Upon entry of the foregoing amendments, claims 26, 33, 117, 122-125, 137-147 and 149-161 are pending in the application, with claim 26 being the independent claim.

Based on the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding objections and rejections and that they be withdrawn.

Objection to the Specification - Sequence listing

The Advisory Action, at page 2, maintained the objection that the present application is not in compliance with the sequence rules. The concern is that the specification describes mutations at several specific positions in a protein without describing the sequence of the protein, and that database reference numbers may change. Applicants have addressed this concern in the manner suggested and accepted by the Examiner in a related case (U.S. Appl. No. 09/245,025, filed February 5, 1999), by amending the specification at page 73, line 13. In view of this

amendment, Applicants respectfully assert that the present application fully complies with the sequence rules under 37 C.F.R. §§ 1.821 through 1.825.

Accordingly, reconsideration and withdrawal of this objection are respectfully requested.

Rejections Under 35 U.S.C. § 103

The Advisory Action, at page 3, maintained the rejection of claims 26, 33, 117, 122-125, 137-147, and 149-161 under 35 U.S.C. § 103 as allegedly being unpatentable over Soltis *et al.* in view of the state of the art at the time the application was filed. Applicants respectfully traverse the rejection.

The pending claims are directed to a method of producing AMV reverse transcriptase by expressing the α and β subunits, ***together in a eukaryotic cell***, and isolating or purifying the expressed reverse transcriptase, such that the resulting AMV reverse transcriptase has a specific activity of at least about 30,000 units per milligram. In the Advisory Action, at page 3, the "Examiner agrees that Soltis *et al.* do not teach the claimed invention." Soltis *et al.* is fatally deficient as a primary reference for at least three reasons:

(1) Soltis *et al.* discloses expressing AMV reverse transcriptase α and β subunits ***individually*** -- NOT TOGETHER,

(2) Soltis *et al.* discloses expressing AMV reverse transcriptase α and β subunits ***in different prokaryotic cells*** – NOT THE SAME EUKARYOTIC CELL,

(3) Soltis *et al.* discloses purifying AMV reverse transcriptase α and β subunits to a specific activity orders of magnitude less than the 30,000 units per milligram recited in the claim.

The deficiencies of Soltis *et al.* cannot be cured by the state of the art in general, or by the Kawa *et al.* and Barr *et al.* references, as the Examiner suggests. The Examiner's unsupported statement that the claimed invention is obvious in view of Soltis *et al.* and the state of the art (as represented by Kawa *et al.* or Barr *et al.*), fails to establish a *prima facie* case of obviousness. The Examiner fails to point to any specific disclosure in Kawa *et al.* or Barr *et al.* that cure the deficiencies of Soltis *et al.* The Examiner fails to points to any specific disclosure in Kawa *et al.* or Barr *et al.* that teaches or suggests the enhanced specific and functional activity of the AMV-RT αβ heterodimer produced by the methods of the claimed invention. Thus, the Examiner has failed to establish a *prima facie* case of obviousness: "deficiencies of the cited reference cannot be remedied by the [PTO]'s general conclusions about what is 'basic knowledge' or 'common sense.'" *In re Lee*, 277 F.3d 1338, 1344 (Fed. Cir. 2002).

Further, a *prima facie* case of obviousness requires a showing that some objective teaching in the prior art or that knowledge generally available to one of skill in the art would lead such an individual to practice the claimed invention. *See In re Fine*, 5 USPQ2d 1596, 1598 (Fed. Cir. 1988). It is not proper to characterize an invention as obvious simply because it is a combination of elements that were known in the art at the time it was made. *See Fromson v. Advance Offset Plate, Inc.*, 755 F.2d 1549, 1556 (Fed. Cir. 1995). Instead, what is needed is a reason, suggestion, or motivation in the prior art that would motivate one of ordinary skill to combine the

cited references, and that would also suggest a reasonable likelihood of success in making the claimed invention as a result of that combination. *See In re Dow Chem. Co.*, 837 F.2d 469, 473 (Fed. Cir. 1988). Once again the Examiner falls short of establishing a *prima facie* case of obviousness. The Examiner provides only an unsupported statement that "one of ordinary skill would have been motivated to carry out the claimed invention" (Advisory Action, page 3) – NOT the required objective reason, suggestion, or motivation in the prior art that would motivate one of ordinary skill to combine the cited references.

Finally, even if the cited references and state of the art could be construed to disclose all of the elements of the presently claimed invention (which they cannot) and even if their disclosures could be properly combined (which they cannot), the presently claimed invention provides a very significant unexpected result: that AMV αβ RT generated by co-expressing α and β together in a eukaryotic cell has a much higher specific and functional activity than AMV αβ RT generated by proteolysis of ββ to αβ when β is expressed alone. Such an unexpected result is a well-accepted indication of nonobviousness. *See Graham v. John Deere Co.*, 86 S.Ct. 684, 694 (1966); *Custom Accessories v. Jeffrey-Allan Industries*, 807 F.2d 955, 960 (Fed. Cir. 1986); *In re Soni*, 54 F.3d 746, 750 (Fed. Cir. 1995).

The surprising and unexpected nature of these results is supported in the accompanying Rule 132 Declaration of Deb K. Chatterjee, Ph.D. ("the Chatterjee Declaration"). Please note that an unsigned copy of the Chatterjee Declaration is provided herein, however a copy executed by Dr. Chatterjee will be filed shortly. For example, the Chatterjee Declaration states that "the RSV αβ RT generated by the co-expression of the α and β genes had a greater than 2 fold increase in specific activity,

a greater than 3.5 fold increase in the total mass of reverse transcriptase product, and a greater than 7 fold increase in the mass of full-length reverse transcriptase product as compared to the RSV αβ RT generated by the expression of the β-subunit alone." Chatterjee Declaration, ¶ 8. Thus, as Dr. Chatterjee states, "it was totally unexpected as of the filing date of the '057 application that RSV αβ RT produced by the co-expression the α subunit and β subunit genes would have a higher specific activity than RSV αβ RT produced by expression of the β-subunit alone, as shown in Table 7." Chatterjee Declaration, ¶ 10. Moreover, as Dr. Chatterjee also states, it was "completely unexpected that RSV αβ RT produced by the co-expression of the α-subunit and β-subunit genes would have had such a substantially higher functional activity than RSV αβ RT produced by expression of the β-subunit alone." *Id.*

These enhanced specific and functional activities of RSV αβ RT produced by the co-expression of the α-subunit and β-subunit genes are shown in Table 7 of the originally filed application. However, as Dr. Chatterjee states, "one of ordinary skill in the art would have understood that the results for specific and functional activities presented in the '057 application for RSV-RT would have been analogous or identical to the results for specific and functional activities for AMV-RT." Chatterjee Declaration, ¶ 11. This expectation of analogous results is at least partly based upon the fact that RSV-RT and AMV-RT are from the same family of reverse transcriptases. As stated in the Chatterjee Declaration,

> Both AMV-RT and RSV-RT are avian sarcoma-leukosis virus (ASLV) reverse transcriptase. As explained in Prasad *et al.*, *Reverse Transcriptase*, Skalka, A.M., and Goff, S.P., Eds., Cold Spring Harbor, New York; Cold Spring Harbor Press, pp. 135-162 (1993), . . . the active form of ASLV-RTs is a heterodimer of one shorter RT

> polypeptide and an incompletely processed RT intermediate, termed the α and β polypeptides, respectively. Thus, the active forms of AMV-RT and RSV-RT share the identical polypeptide subunit components.

Chatterjee Declaration, ¶ 11.

In addition to being from the same family of reverse transcriptases, AMV-RT and RSV-RT also share greater than 95 percent homology at the amino acid level. As stated in the Chatterjee Declaration, "[b]ecause AMV-RT and RSV-RT are from the same family of retroviral reverse transcriptases (ASLV-RT) and have greater than 95 percent homology at the amino acid level, it is my opinion that one of ordinary skill in the art would understand that the results for specific and functional activities presented in the '057 application for RSV-RT could be extrapolated to, and therefore be representative of, the expected results for specific and functional activities in AMV-RT." Chatterjee Declaration, ¶ 12. Thus, in the view of a person of ordinary skill in the art it, is unquestionable that the unexpected results generated for RSV αβ RT would be understood to represent analogous unexpected results for AMV αβ RT, such as that produced by the presently claimed methods.

Accordingly, it is clear that the present invention provides results that were not expected in view of knowledge in the art as of the filing date of the present application, which the Federal Circuit has recognized as "[o]ne way for a patent applicant to rebut a *prima facie* case of obviousness. . . ." *Soni*, 54 F.3d at 750. Further, these results were unexpected compared to the closest prior art cited by the Examiner (*i.e.*, Soltis in view of Kawa and Barr), which is the standard for judging unexpected results in an obviousness context. *See In re De Blauwe*, 736 F.2d 699, 705 (Fed. Cir. 1984); *In re Baxter Travenol Labs.*, 952 F.2d 388, 392 (Fed. Cir. 1991). Moreover, and even more indicative of the unexpected nature of these results, is that

these results were unexpected in view of the disclosure of Stewart *et al.* (of record in the present application as Document AT 23), which Applicants view as closer art than that cited by the Examiner. Thus, Applicants have established the unexpected nature of the discovery that the production of an AMV αβ RT by the co-expression of the α and β genes together in the same cell has a significantly higher specific and functional activity than an AMV αβ RT produced by the expression of the β gene alone.

Therefore, even if a *prima facie* case of obviousness could be established based on the cited art (which it cannot), Applicants have successfully rebutted and overcome the Examiner's assertion of obviousness. Applicants therefore respectfully assert that the presently claimed methods are non-obvious over the cited art. Accordingly, reconsideration and withdrawal of this rejection are respectfully requested.

Conclusion

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. Applicants believe that the present application is in condition for immediate allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

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